The Human Microbiome: The Interface of Health and Disease

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artwork by Scott Draves (www.electricsheep.org)
The presenter declares that his only funding/financial interest involving the microbiome is as editor of a Springer book series (Molecular and Integrative Toxicology) that includes the microbiome among its titles.

He received no compensation in connection to his appearance in the documentary film, Microbirth.
OUTLINE

• Completing the Human-Microbial Superorganism (i.e., seeding)
• Role of Self-Completion, Immune Maturation and Tolerance
• Second Genome Management: the New Frontier (i.e., feeding, cultivation, and pruning)
• New Benefit: Risk Equations and Treatment Horizons
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Challenge

If you could pick ONE sign that best distinguishes a lifetime of health from that of disease ......what would that be?

My answer for the sign: Self-completion of the human-microbial superorganism

Challenge was issued for an invited paper for a special issue of the physics journal *ENTROPY*
Self-Completion - The Completed Self

Host-specific, Family-sourced microbiota

The Completed Self: An Immunological View of the Human-Microbiome Superorganism and Risk of Chronic Diseases

*Entropy* 2012, 14 (11), 2036-2065

R Dietert, J Dietert
Ramifications of Incompleteness
(Defective Human-Microbial Superorganism)

Inadequate microbial seeding at birth (newborn incompleteness)

The incomplete newborn is programmed to be metabolically and immunologically deficient.

Microbirth
a new documentary film
Monophyletic strains of:
*Bifidobacterium adolescentis* (4 strains)
*B. bifidum* (7 strains)
*B. catenulatum* (1 strain)
*B. longum subsp. longum* (7 strains)
*B. Pseudocatenulatum* (2 strains)

found in the mother’s GI tract were transferred to the infant’s GI tract via vaginal (11 out of 12) but not Cesarean delivery (0 of 5). There was no evidence of horizontal transfer of specific strains among nine babies born in the same hospital.

The Complete Human: Three Domains of Life

Domains of Life
- Eukaryota
- Bacteria
- Archaea

Genomes
- First
  - ~25,000 genes
- Second
  - ~10 million genes

Superorganism
- Majority-Microbial Humans

Composition
- Approximately 90% microbial by cell number
Archaea – also in your gut
Breathalyzer and Urinary Tests for the Microbiome VOCs & Gases and Differential Disease States

Children living near a sanitary landfill had elevated breath methane correlated with elevated methane producing Archaea in the gut microbiome.

(unrelated to socio economic status)


Volatile organic compounds (VOCs) in urine can be used to differentiate coeliac from irritable bowel syndrome based on distinctive microbiome-produced metabolites.

Microbial Dysbiosis and Impending *C. Difficile* Outbreaks

Who are you really? and.... How (healthy) are you?
Brain – Who’s Running the Show?

Neurobehavior
Kin recognition
Mating behavior

Food preferences and cravings

Microbial metabolites including short-chain fatty acids

See:
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Managing the Human Ecosystem for Effective Immune Tolerance

Ineffective Microbiome-Mediated Immune Maturation  

Effective Microbiome-Mediated Immune Maturation
Gut Microbial Dysbiosis – Immune Dysfunction

**Invariant NKT cells**
- population size – regulation of inflammation
- Risk of autoimmune and inflammatory disease

**Dendritic cells**
- maturation promoting T helper balance
- control of adaptive immune responses
- Risk of allergic and inflammatory disease

**Macrophages**
- role in inflammation and balance of polarization
- Risk of inflammatory disease, heart disease, and cancer

**Natural (FoxP3+, CD25+) T regulatory cells**
- maturation and expansion capacity to control Th17 cells
- Risk of autoimmune, allergic and inflammatory disease

**Gut Microbiota**
Microbiome Dysbiosis Affecting Airway Macrophages and Allergic Disease

Antibiotic administration (mice) →
Candida species fungal overgrowth in gut (increased PGE2 production) →
Distant M2 polarization of macrophages in the airways →
Allergic airway inflammation

Noncommunicable Diseases and Conditions (NCDs) are the Greatest Threat to Sustainable Healthcare

• Already the Number #1 Cause of Mortality Worldwide (63%)*

• Dramatically Impacts Both Productivity and Quality of Life

• Estimated to Cost 48% of Global GDPs by 2030*

• Most Chronic Diseases are Increasing in Prevalence

• 45.3% of all US adults age 65 and above have two or more chronic diseases: a 20% increase from the previous decade.*
Misregulated Inflammation

A tie that binds non-communicable diseases and conditions (NCDs) together

- Most NCDs feature misregulated (unresolved) inflammation.

- Resolving the inflammation appears to reverse the course of multiple chronic diseases involving different tissues or organs (e.g., action of resolvins).
Life Course of Comorbid Chronic Diseases With Increased Aging

Dietert, R in (Ed) Weiss, B.  
*Aging and Vulnerability to Environmental Chemicals.*  
Royal Soc. of Chemistry Press. 2013
Address Diseases via the Microbiome

**Respiratory Disease**

Microorganism-induced suppression of allergic airway disease: novel therapies on the horizon?


**Gastrointestinal Disease**

Enteric microbiota leads to new therapeutic strategies for ulcerative colitis.


**Metabolic Disease**

Intestinal microbiota and faecal transplantation as treatment modality for insulin resistance and type 2 diabetes mellitus.

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Second Genome Management Across a Life Course
Planning at Different Life Stages for Microbiome Management and Health Risk Reduction

- Diabetes, Obesity, Colitis, Asthma, Celiac disease
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**Microbiome Adjustment as Part of Disease Management**

- Microbiome adjustment for pregnancy and to optimize microbiome seeding

**Birth: Vaginal vs. Caesarean Delivery**

- Healthy microbiome seeding plan

**Feeding the Microbiota for Optimized Immune and Microbial Co-maturation**

- Reduced risk for various immune dysfunction-promoted NCDs among present and future generations
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Environmental chemicals and drugs reported to affect the gut microbiome

- *Heavy metals* (e.g., cadmium, lead, arsenic)
- Other metals (iron, selenium, zinc)
- PCBs (Choi et al., EHP 2013)
- Particulate matter (PM10) (Kish et al. PloS One 2013)
- Chloryrifos (Joly et al., ESPRI, 2013)
- High fat diet (Myles et al. PloS One 2014)
- Valproate (de Theije et al. Brain Behav Immun 2013)
- Antibiotics (Ng et al., Nature 2013; Faa et al., J Matern Fetal Neonatal Med. 2013)
- Vitamin D (Ooi et al., J.Nutr 2013)
Responses of the Microbiota to Environmental Exposures

Environmental pollutants (e.g., metals, organics)

1. Sequestration
2. Avoidance/Exclusion
3. Metabolism
4. Specific Signaling
5. Selective Microbe Death
6. Selective Microbe Expansion
7. Translocation

From: NRC, Environ Health Perspect, 1987

From: Dietert and Silbergeld, Toxicol. Sci., in press, 2015
The Microbiome in Disease States and Altered Environmental Vulnerability

Cesarean Delivery ➔ Antibiotic Use ➔ Maternal Gestational Weight ➔ Cadmium Exposure ➔ Air Pollution

Reduced diversity of gut microbiota and/or altered gut microbe metabolism

Altered Fatty Acid Production ➔ Epigenetic Gene Regulation ➔ Obesity/High Body Mass Index

Altered impact of air pollution on risk of hypertension ➔ Altered iron content and distribution in macrophages ➔ Altered body burden/distribution of arsenic

From: Dietert and Silbergeld, Toxicol. Sci.in press, 2015; See also Ginsberg et al. Curr Environ Health Report, 2014
New Horizons: Evaluation and Treatment?*

- Microbiome Fingerprinting
  - Detailed personalized analysis of the microbiome
- Microbiome Modification
  - Prebiotics and Probiotics
  - Fecal microbiota transfer
  - Direct microbial metabolite treatment
- Microbiome Support, Protection, and Treatment Routes
  - Supportive diet for microbiota instillation and maintenance
  - Avoidance of harmful drugs and chemicals based on superorganism vulnerability (not just mammalian cell sensitivity).
  - New therapeutics that work via the Microbiome

*Timing is everything to avoid perinatally-programmed, life-long immune dysfunction
1. The human–microbial superorganism is the actual target organism for: dietary strategies, drug and medical therapies, health protection and safety evaluation, and pregnancy, birth, and infant perinatal planning.

2. Effective newborn self-completion and protection begins during pregnancy and continuing in early neonatal is critical for health across the life course.

3. The “90%” is likely to be a new point of emphasis across multiple disciplines as we seek comprehensive and long-term strategies for reduced risk of NCDs and as well as multi-drug resistant infections.
Acknowledgements

• Dr. Ellen Silbergeld, Johns Hopkins School of Public Health
coa-author and co-developer of the new environmental health model

• Janice Dietert, Performance Plus Consulting
coa-author and editor
Thank You

Questions?